Clinical and Hemodynamic Determinants of Left Ventricular Dimensions

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• This study was designed to quantitate the influence of 20 clinical, hemodynamic, and volume determinants of left ventricular (LV) structure. Systemic hemodynamics, intravascular volume, and LV echocardiographic measurements were collected in a heterogeneous population of 171 patients. Stepwise multiple-regression analysis indicated that body weight and body-surface area were the most powerful determinants of LV chamber size, wall thickness, and muscle mass. Age, a pressure independent determinant of myocardial mass, had no influence on chamber size or LV function. Arterial pressure correlated best with the relative wall thickness and chamber volume. Intravascular volume was a major discriminator for chamber volume, LV mass, and velocity of circumferential fiber shortening. It is concluded that body weight, arterial pressure, intravascular volume, and age are each independent determinants of the LV dimension. Systolic pressure most closely correlated with relative wall thickness and thereby is the best predictor of degree of concentric LV hypertrophy.

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Left ventricular performance is determined by preload, myocardial contractility, heart rate, and afterload. Homeostasis of cardiac function as well as its instantaneous response to changing physiologic requirements is regulated by a delicate interplay among these determinants.[1] Any major imbalance among them, if persisting for a prolonged period of time, should lead to a structural adaptation of the myocardium. Thus, the left ventricle will respond to a persistently elevated afterload, such as that occurring in arterial hypertension with progressive concentric left ventricular hypertrophy.[2-10] By the same token, a prolonged elevated preload, such as that which occurs in a physiologic (during pregnancy or exercise) or pathologic (obesity) volume overload state will lead to chamber enlargement and gradual eccentric ventricular hypertrophy.[11-15]

A variety of clinical, hemodynamic, fluid volume, and endocrine disorders have been shown to affect the four major determinants of left ventricular function and thus, ultimately, left ventricular structure. The present study was designed to evaluate 20 clinical, hemodynamic, and fluid volume variables as potential determinants of left ventricular structure.

SUBJECT AND METHODS

Study Population

The present study comprised a heterogeneous population of 171 patients whose clinical characteristics are detailed in Table 1. Desirable or ideal body weight was defined by standards of the Metropolitan Insurance Company, and the patient's body weight was expressed as percentage deviation from the ideal weight.[16] Clinical examination of patients and definition of hypertension were performed as previously reported.[17] Significant coronary artery disease was excluded by clinical criteria and by exercise tolerance tests in conjunction with radionuclide studies if indicated. Most patients never had been treated for high BP previously, and in those who had been, the antihypertensive medication was discontinued at least four weeks prior to the study. We purposely selected a heterogeneous population with old and young, lean and obese, as well as normotensive and hypertensive subjects. Age ranged from 13 to 81 years, body weight from 43 to 186 kg (from −21% to 145% overweight), and arterial pressure from 94/56 to 225/149 mm Hg. The protocol for the study was approved by our Clinical Investigation Committee, and an informed consent was obtained from each individual.

Hemodynamics

Systemic hemodynamics were measured as previously reported.[17] Briefly, cardiac output was measured in triplicate with indocyanine green, and intra-arterial pressure was obtained by a catheter with its tip in the subclavian artery or aortic arch. Mean arterial pressure was obtained by electrical integration, and standard hemodynamic indexes were calculated. Plasma volume was determined during the hemodynamic study by injecting iodine 125–labeled serum albumin and measuring the decline of the plasma radioactivity after 15 and 30 minutes of equilibration.[17] Red cell mass was measured simultaneously with chromium 51–labeled RBCs, and total blood volume was calculated as the sum of plasma volume and RBC mass.

Echocardiography

Standard methods of M-mode echocardiography were employed as previously reported[3] by using an ultrasonoscope (Smith-Kline Ecoline 28) interfaced with a strip chart recorder (Honeywell) and a probe measuring 1.27 cm in diameter. Septal wall thickness and posterior wall thickness were measured in standard fashion.[18,19] The mean circumferential fiber shortening rate was calculated by using the method of McDonald et al,[19] with the ejection time taken from an average of 10 cycles. Relative wall thickness was determined by dividing posterior left ventricular wall thickness by half of the end-diastolic diameter.[20] Left ventricular mass was calculated according to the formula of Bennett and Evans.[21] Since this formula tends to overestimate left ventricular mass, the regression equation of Devereux and Reicheck[22] was used in Table 2 to correct this and to allow comparison with data from other laboratories. For classification of the patients, we defined left ventricular hypertrophy (LVH) empirically as a posterior wall thickness exceeding 11 mm. All echocardiograms were read by two independent observers.

Statistics

Statistical comparison between normotensive subjects and hypertensive patients with and without LVH was made by a two-way analysis of variance[23] (Tables 1 and 2). To weigh or quantitate the influence of various indexes on left ventricular structure, a stepwise multiple-regression analysis (Statistical Package for Social Sciences) was performed[23] with 11 directly measured independent

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Table 1.—Clinical and Hemodynamic Characteristics of the Study Population*

Characteristic	Normotensive		Hypertensive		Analysis of Variance	
	Without LVH	With LVH	Without LVH	With LVH	N/H	−/+
No.	52	22	56	41		
Age, yr	35.4±12.6	38.5±14.4	41.1±13.9	46.1±15.9	.02	NS
Race, B:W	15:37	3:19	15:41	21:20	.04	NS†
Sex, M:F	22:30	4:18	30:26	17:24	.04	.02
Height, cm	170.1±9.7	175.5±9.4	168.9±8.0	170.4±9.7	.05	.03
Weight, kg	78.3±26.8	99.8±20.3	76.8±18.7	86.0±23.6	.03	.0001
Body surface area, sq m	1.88±0.28	2.14±0.24	1.87±0.22	1.95±0.21	.01	.0001†
% of ideal weight	+27.1±32.0	+49.7±24.9	+27.9±32.2	+35.0±30.2	NS	.005
Systolic pressure, mm Hg	130.8±14.5	130.9±12.4	163.1±19.1	170.0±22.3	. . .	. . .
Diastolic pressure, mm Hg	75.5±7.16	75.6±6.6	95.2±12.1	95.4±12.9	. . .	. . .
Mean arterial pressure, mm Hg	93.8±8.6	94.1±7.3	117.8±12.3	120.2±13.9	. . .	. . .
Heart rate, beats per min	69.3±9.4	66.7±10.8	72.8±12.8	68.6±9.2	NS	NS
Cardiac output, 1/min	5.99±1.48	6.62±1.50	5.75±1.29	5.64±1.15	.01	NS
Cardiac index, 1/min/sq m	3.20±0.57	3.07±0.50	3.10±0.64	2.85±0.50	NS	.05
Total peripheral resistance, mm Hg/1/min	16.3±4.4	14.9±3.7	21.2±5.1	22.7±5.7	.0001	NS
Left ventricular stroke work, units	152±45	172±30	170±36	183±42	.03	.02
Total blood volume, mL	4,629±968	5,416±1,111	4,361±884	4,808±1,017	.01	.001
Plasma volume, mL	2,877±601	3,250±524	2,743±557	3,051±642	NS	.001
Renal blood flow, mL/min	1,032±424	983±573	844±320	799±378	.02	NS

*LVH indicates left ventricular hypertrophy (posterior wall thickness >11 mm); N/H, difference between all normotensive and all hypertensive patients, regardless of classification by presence or absence of LVH; and −/+, difference between subjects with and without LVH, regardless of classification according to arterial pressure.

†Significant interaction between the effects of hypertension and the ones of obesity.

Table 2.—Echocardiographic Left Ventricular Dimensions*

Characteristic	Normotensive		Hypertensive		Analysis of Variance	
	Without LVH	With LVH	Without LVH	With LVH	N/H	−/+
Diastolic dimension, cm	5.27±0.83	5.86±1.09	4.92±0.79	5.21±0.87	.001	.005
Systolic dimension, cm	3.35±0.68	3.76±0.95	3.08±0.69	3.27±0.74	.002	.014
Posterior wall thickness, cm	0.90±0.14	1.30±0.11	0.94±0.12	1.29±0.11	NS	†
Septal thickness, cm	1.01±0.19	1.32±0.16	1.01±0.22	1.30±0.24	NS	.0001
Left ventricular mass, g	227±84	418±136	209±78	356±107	NS	.0001
Corrected left ventricular mass, g	174	302	162	261	. . .	. . .
Relative wall thickness	0.39±0.27	0.46±0.11	0.39±0.07	0.51±0.10	NS	.0004
Fractional fiber shortening ratio	36.4±7.7	36.4±8.1	37.6±8.7	37.1±9.9	NS	NS
Velocity of circumferential fiber shortening, circumferences/s	1.19±30	1.15±32	1.21±31	1.17±32	NS	NS

*LVH indicates left ventricular hypertrophy (posterior wall thickness >11 mm); N/H, difference between all normotensive and all hypertensive patients, regardless of classification by presence or absence of LVH; and −/+, difference between subjects with and without LVH, regardless of classification according to arterial pressure.

†This was significant by design.

clinical determinants (age, sex, race, body weight, and body height), and hemodynamic determinants (systolic, diastolic, heart rate, cardiac output, renal blood flow, and total blood volume). Correction for sample size, total number of determinants, and number of selected determinants was done according to Wilkinson.[24] A second multiple-regression analysis was calculated by adding derived indexes such as body surface area, mean arterial pressure, total peripheral and renal vascular resistance, stroke work, stroke volume, mean left ventricular ejection rate, plasma volume, and RBC mass. Since a complete set of data was available for 158 patients, both multiple-regression analyses included 158 patients, whereas most all other calculations (except for plasma volume, total blood volume, RBC mass, and renal blood flow) were done with 171 patients. Since potentially the selection of the present population could introduce a bias, we recalculated both multiple analyses after excluding all patients older than 65 years, those who were more than 50% overweight, and those whose systolic pressure exceeded 180 mm Hg. Moreover, simple bivariate (linear) regression analyses were calculated between clinical, hemodynamic, as well as fluid volume determinants (measured values only) and echocardiographic indexes.[23]

RESULTS

Body Weight, Height, Surface Area, and Age

Weight emerged as a major discriminator for five of all eight echocardiographic measures (Table 3). It exerted its strongest influence on structural measurements such as wall thickness, diastolic diameter, left ventricular mass, and septal thickness. In contrast, left ventricular contrac-

Table 3.—Analyses Between Clinical, Hemodynamic, and Echocardiographic Findings

	Multiple Regression Analysis I (n=158)	β*	Bivariate Analysis (n=171)	r*
Internal diastolic diameter ($F=10.638$; $P<.05$)	Weight	.261	Weight	.395
	Diastolic pressure	−.236	Total blood volume	.384
	Heart rate	−.159	Stroke volume	.334
	Total blood volume	.104	Mean arterial pressure	−.275
	Cardiac output	.084	Diastolic pressure	−.272
Internal systolic diameter ($F=11.812$; $P<.05$)	Total blood volume	.292	Total blood volume	.425
	Diastolic pressure	−.149	Weight	.379
	Weight	−.189	Stroke volume	.285
	Cardiac output	−.177	Mean arterial pressure	−.283
	Systolic pressure	.135	Renal blood flow	.279
Posterior wall thickness ($F=10.983$; $P<.05$)	Weight	.302	Weight	.358
	Systolic pressure	.205	Age	.303
	Total blood volume	.200	Total blood volume	.274
	Age	.192	Systolic pressure	.230
	Cardiac output	−.075	Mean arterial pressure	.181
Left ventricular mass ($F=11.670$; $P<.05$)	Weight	.255	Weight	.452
	Total blood volume	.248	Total blood volume	.444
	Age	.161	Stroke volume	.291
	Heart rate	−.084	Sex	−.273
	Diastolic pressure	.074	Heart rate	−.250
Relative wall thickness ($F=10.252$; $P<.05$)	Systolic pressure	.390	Systolic pressure	.421
	Weight	.120	Mean arterial pressure	.345
	Age	.093	Diastolic pressure	.315
	Heart rate	.081	Age	.247
Septal thickness ($F=11.210$; $P<.01$)	Weight	.320	Weight	.298
	Age	.260	Age	.303
	Systolic pressure	.095	Stroke work	.215
			Total blood volume	.172
			Systolic pressure	.156
Velocity of circumferential fiber shortening ($F=6.815$; $P<.05$)	Total blood volume	−.313	Total blood volume	−.220
	Cardiac output	.156	Heart rate	.165
			Weight	−.141
Fractional fiber shortening ($F=9.006$; $P<.01$)	Total blood volume	−.236	Total blood volume	−.234
			Height	−.177
			Systolic pressure	.170
			Weight	−.142
			Mean arterial pressure	.141

*β indicates standardized regression coefficient; r, linear regression coefficient.

tile function as measured by velocity of circumferential fiber shortening or fractional fiber shortening was not significantly affected by body weight. Also, patients with LVH were significantly ($P<.01$) heavier than those with posterior wall thickness of less than 11 mm regardless of arterial pressure.

Body height alone did not evolve as a significant discriminator. However, body surface area replaced body weight as the most powerful discriminator for diastolic diameter ($r=.468$), posterior wall thickness ($r=.287$), septal thickness ($r=.444$), and left ventricular mass ($r=.365$) in the second multiple-regression analysis (in which derived indexes were included). In all but one instance (posterior wall thickness), standardized regression coefficients for body surface area were higher than the one for weight alone in the first multiple-regression analysis.

All dependent variables of left ventricular wall thickness as well as the relative wall thickness showed age dependency. In contrast, the systolic and diastolic measures of chamber volume were independent of age. Also, age had no substantial effect on left ventricular contractile function as measured by the fractional fiber shortening rate or velocity of circumferential fiber shortening.

Hemodynamics and Intravascular Volume

Systolic or diastolic pressures significantly influenced five of six dependent variables of left ventricular structure (Table 3). Systolic pressure was the most powerful discriminator for the relative wall thickness. In contrast, left ventricular function was not affected by arterial pressure.

Total blood volume emerged as the most potent determinant of velocity of circumferential fiber shortening and fractional fiber shortening. Moreover, it also significantly influenced systolic and diastolic dimension (chamber volume) as well as wall thickness and left ventricular mass (Table 3).

Cardiac output was a significant discriminator for chamber volume, left ventricular wall thickness, septal thick-

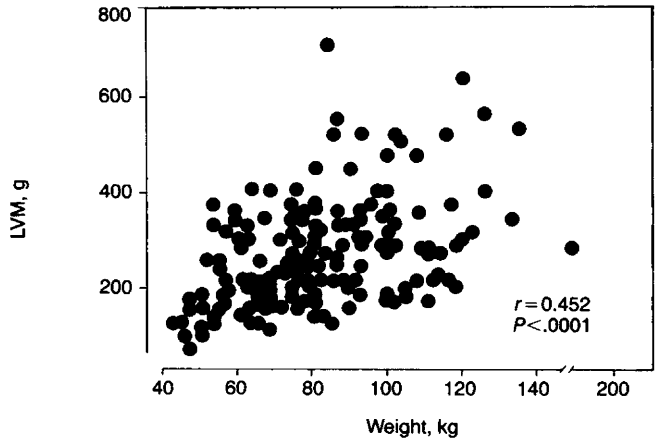

Fig 1.—Correlation between body weight and left ventricular mass (LVM).

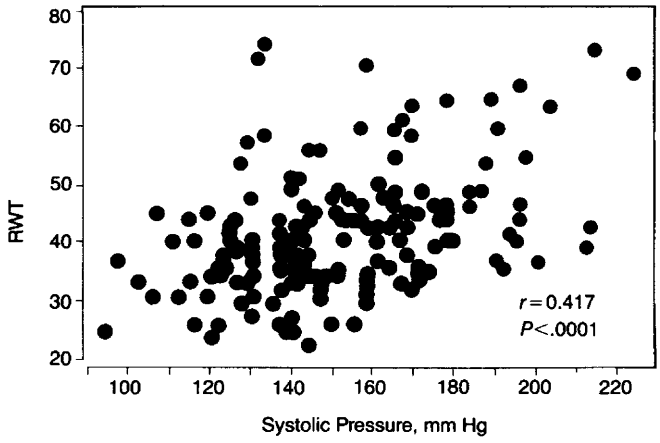

Fig 2.—Correlation between systolic pressure and relative wall thickness (RWT). Increase in relative wall thickness with pressure indicates progressive concentric hypertrophy.

ness, and velocity of circumferential fiber shortening. However, statistical significance of the correlations was relatively weak for all these dependent variables (Table 3).

Total peripheral resistance became a significant independent variable for posterior wall thickness ($r = .236$), replacing systolic pressure in the second multivariate analysis (in which derived indexes were used). All other echocardiographic measurements were not directly influenced by total peripheral resistance.

Recalculating both analyses after omitting patients that were older than 65 years or more than 50% overweight, single or combined, did not significantly influence the relative value of standardized regression coefficients.

Bivariate Linear Regressions

Surprisingly, a very similar picture emerged when bivariate linear regression analyses were calculated between the same variables (Table 3). Body weight, age, total blood volume, and, to a lesser degree, arterial pressure and body height emerged as independent variables correlating closest with echocardiographic indexes. The closest correlations were observed between body weight and LV mass ($r = .452$, $P < .0001$) (Fig 1), total blood volume and systolic ventricular diameter ($r = .425$, $P < .0001$), as well as between systolic pressure and relative wall thickness ($r = .421$, $P < .0001$) (Fig 2).

COMMENT

The principal findings of the present study indicate that left ventricular structure is influenced mostly by body weight (or body surface area), age, and intravascular volume. Arterial pressure, while strongly affecting the relative wall thickness and chamber volume, had less influence on absolute wall thickness and myocardial mass. Left ventricular contractile function was mainly under the influence of total blood volume and systemic flow.

Body Weight and Total Blood Volume

That body weight (or body habitus) evolved as the major determinant of left ventricular structure should not be surprising. Indeed, Devereux et al[25] and Wahr et al[26] most recently reported a similar close relationship between body surface area and left ventricular mass in normal populations. Increased body weight such as that seen in exogenous obesity augments metabolic demand and thus, in turn, cardiac output.[11,15,27-32] Since heart rate is not usually affected by being overweight, the elevated cardiac output is mainly produced by an expanded stroke volume. An increase in stroke volume, together with expanded cardiopulmonary and total blood volumes, has been observed in obese patients and serves to elevate left ventricular preload.[15,31] The left chamber initially responds to a chronically elevated preload with dilatation to accommodate the higher filling volume. According to LaPlace's Law, chamber dilatation also increases left ventricular wall stress and therefore afterload. The left ventricle adapts to these stresses by increasing myocardial mass in proportion to chamber dilatation. Indeed, eccentric LVH has been documented in obese patients who were matched with regard to mean arterial pressure, age, sex, and race with lean subjects.[15] A close correlation between body weight and left ventricular mass was observed in our study (Fig 1).

In the present report, most normotensive patients who fulfilled echocardiographic criteria for left ventricular hypertrophy (posterior wall thickness >1.1 cm) were moderately to distinctly overweight. Left ventricular stroke work was elevated in these normotensive subjects (Table 1), reaching about the same level as in nonobese patients with essential hypertension. Unlike in hypertension, where stroke work is elevated because of the increase in systolic pressure, the heart of an overweight (and otherwise "normal") patient has to deal with an increased stroke work because of the expanded stroke volume.[32]

Age

Aging also has been related to an increased cardiac mass documented to affect specifically cardiovascular function and structure.[33-35] Although resting ventricular function is usually well maintained throughout senescence, a slight decline of cardiac index of about 25 mL/min/sq m/yr has been found in various invasive studies.[36-38] This decline in systemic flow has been found to be associated with an increase in left ventricular wall thickness and left ventricular mass without affecting chamber volume.[39,40] Gerstenblith et al[34,39] reported a positive correlation between posterior wall thickness and age in a population that was free of cardiovascular disease, in particular free of coronary heart disease and hypertension. A more recent study indicated a more gradual age-related increase in wall thickness closely paralleling the upward drift in arterial pressure with age.[41] In contrast, Valdez et al[42] did not find any age-dependent changes in echocardiographic data in a population with a more narrow age range.

The following three main factors could contribute to this phenomenon of "LVH" related to aging:

1. Arterial pressure increases throughout life even within the normotensive range in westernized populations.
2. Arterial compliance decreases and total peripheral resistance increases with age, both of which are determinants of aortic input impedance. These changes may occur independently of the level of arterial pressure.
3. Contractile myocardial fibers are gradually interspersed with inactive tissue so that the remaining contractile elements are stimulated to hypertrophy. In addition, subclinical amyloidosis or other myocardial degenerative disorders may contribute to the increase in left ventricular mass with aging.

Since arterial pressure increases with age, one might argue that the augmented afterload would be the predominant pathogenetic factor serving to lower cardiac output and to increase relative wall thickness. However, the present study clearly establishes that the age-dependent increase in myocardial mass occurs independently of changes in arterial pressure.

Arterial Pressure

One might logically suppose that the relationship between the level of arterial pressure and left ventricular mass would be a close one. Early necropsy studies did indeed show a close correlation between arterial pressure and left ventricular mass.[43] However, recent clinical data indicated that left ventricular adaptation to a given pressure load can be modified by a variety of other pathogenic factors. The present study included a number of obese and elderly subjects in whom left ventricular hypertrophy often is found even in the absence of arterial hypertension. Nevertheless, systolic pressure remained the most powerful determinant of the relative wall thickness—a measure of concentric left ventricular hypertrophy—and also closely correlated with posterior wall thickness (Fig 2). These structural adaptations, however, seem not to be confined to the adult population. Most recently, Culpepper and coworkers[44] documented concentric hypertrophy on the M-mode echocardiogram even in children whose BP was elevated only to the borderline level.

Richard B. Devereux made a critical review of this study.

References

1. Mason DT: Regulation of cardiac performance in clinical heart disease: Interactions between contractile state mechanical abnormalities and ventricular compensatory mechanisms. *Am J Cardiol* 1973;32:437-446.
2. Gaasch WH: Left ventricular radius to wall thickness ratio. *Am J Cardiol* 1979;43:1189-1194.
3. Dunn FG, Chandraratna PAN, DeCarvalho JGR, et al: Pathophysiological assessment of hypertensive heart disease with echocardiography. *Am J Cardiol* 1977;39:789-795.
4. Savage DD, Drayer JIM, Henry WL, et al: Echocardiographic assessment of cardiac anatomy and function in hypertensive patients. *Circulation* 1979;59:623-632.
5. Cohen A, Hagan AD, Watkins J, et al: Clinical correlates in hypertensive patients with left ventricular hypertrophy disguised with echocardiography. *Am J Cardiol* 1981;47:335-341.
6. Schlant RC, Felner JM, Blumenstein BA, et al: Echocardiographic studies of left ventricular anatomy and function before and after treatment of essential hypertension, abstracted. *Am J Cardiol* 1977;39:296.
7. Devereux RB, Pickering TG, Harshfield GA, et al: Left ventricular hypertrophy in patients with hypertension: Importance of blood pressure response to regularly recurring stress. *Circulation* 1983;68:470-476.
8. Devereux RB, Savage DD, Sachs I, et al: Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. *Am J Cardiol* 1983;51:171-176.
9. Rowlands DB, Glover DR, Ireland MA, et al: Assessment of left ventricular mass and its response to antihypertensive treatment. *Lancet* 1982;1:467-470.
10. Al-Nouri MB, Ford LE, Wix H: Dimensional correlates of left ventricular dilation in the presence of hypertrophy. *Chest* 1983;83:43-49.
11. Messerli FH: Cardiovascular effects of obesity and hypertension. *Lancet* 1982;1:1165-1168.
12. Rubler S, Damani PM, Pinto ER: Cardiac size and performance during pregnancy estimated with echocardiography. *Am J Cardiol* 1977;40:534-540.
13. Woodard CB, Quinones MA, Alexander JK: Pathogenesis of myocardial dysfunction in extreme obesity. *Circulation* 1978;58(suppl 2):230-239.
14. Katz R, Karliner JS, Resnik R: Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation* 1978;58:434-441.
15. Messerli FH, Sundgaard-Riise K, Reisin E, et al: Dimorphic cardiac adaptation to obesity and arterial hypertension. *Ann Intern Med*, in press.
16. New Weight Standards for Men and Women. Statistical Bulletin. New York, Metropolitan Life Insurance Company, 1959, vol 40, p 1.
17. Messerli FH, deCarvalho JGR, Christie B, et al: Systemic and regional hemodynamics in low, normal and high cardiac output borderline hypertension. *Circulation* 1978;58:441-448.
18. Sahn DJ, DeMaria A, Kisslo J, et al: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-1085.
19. McDonald IG, Feigenbaum H, Chang S: Analysis of left ventricular wall motion by reflected ultrasound: Application to assessment of myocardial function. *Circulation* 1972;46:14-25.
20. Ford LE: Heart size. *Circ Res* 1976;39:297-303.
21. Bennett DH, Evans DW: Correlation of left ventricular mass determined by echocardiography with vector cardiographic and electrocardiographic voltage measurement. *Br Heart J* 1974;36:981-987.
22. Devereux RB, Reicheck N: Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. *Circulation* 1977;55:613-618.
23. Snedecor GW, Cochran WG: *Statistical Methods*, ed 6. Ames, Iowa, State University Press, 1967.
24. Wilkinson L: Stepwise regression. *Psychol Bull* 1979;86:168-174.
25. Devereux RB, Casale PN, Kligfield P, et al: Normalization of left ventricular anatomic measurements, abstracted. *Clin Res* 1983;31:178.
26. Wahr DW, Wang Y-S, Heilbron D, et al: Clinical quantitative echocardiography: III. Left ventricular mass in a normal adult population, abstracted. *Clin Res* 1982;30:23.
27. Alexander JK, Peterson KL: Cardiovascular effects of weight reduction. *Circulation* 1972;45:310-318.
28. Backman L, Freyschuss U, Hallberg D, et al: Cardiovascular function in extreme obesity. *Acta Med Scand* 1973;193:437-445.
29. Messerli FH, Christie B, DeCarvalho JGR, et al: Obesity and essential hypertension: Hemodynamics, intravascular volume, sodium excretion, and plasma renin activity. *Arch Intern Med* 1981;141:81-85.
30. Kaltman AJ, Goldring RM: Role of circulatory congestion in the cardiorespiratory failure of obesity. *Am J Med* 1976;60:645-653.
31. Devitis O, Fazio S, Petitto M, et al: Obesity and cardiac function. *Circulation* 1981;64:477-482.
32. Messerli FH, Sundgaard-Riise K, Reisin E, et al: Disparate cardiovascular effects of obesity and arterial hypertension. *Am J Med* 1983;74:808-812.
33. Lakatta EG: Alterations in the cardiovascular system that occur in advanced age. *Fed Proc* 1979;38:163-167.
34. Gerstenblith G, Weisfeldt ML, Lakatta EG: Age changes in myocardial function and exercise response. *Prog Cardiovasc Dis* 1976; 19:1-21.
35. Weisfeldt M: Aging of the cardiovascular system. *N Engl J Med* 1980;303:1172-1173.
36. Brandfonbrener M, Landowne M, Shock NW: Changes in cardiac output with age. *Circulation* 1955;12:557-566.
37. Strandell T: Circulatory studies on healthy old men. *Acta Med Scand Suppl* 1964;175:1-44.
38. Conway J, Wheeler R, Sannerstedt R: Sympathetic nervous activity during exercise in relation to age. *Cardiovasc Res* 1971;5:577-581.
39. Gerstenblith G, Frederiksen J, Yin FCP, et al: Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56: 273-278.
40. Gardin JM, Henry WL, Savage DD, et al: Echocardiographic measurements in normal subjects: Evaluation of an adult population without clinically apparent heart disease. *J Clin Ultrasound* 1979;7:439-447.
41. St John Sutton MG, Reicheck N, Lovett J, et al: Effects of age, body size and blood pressure on the normal human left ventricle, abstracted. *Circulation* 1980;62:305.
42. Valdez RS, Motta JA, London E, et al: Evaluation of the echocardiogram as an epidemiologic tool in an asymptomatic population. *Circulation* 1979;60:921-929.
43. Evans G: A contribution to the study of arteriosclerosis, with special reference to its relation to chronic renal disease. *Q J Med* 1921;14:215-282.
44. Culpepper WS III, Sodt PC, Messerli FH, et al: Cardiac status in juvenile borderline hypertension. *Ann Intern Med* 1983;98:1-7.